Pain Catastrophizing and Fear of Pain predict the Experience of Pain in Body Parts not targeted by a Delayed-Onset Muscle Soreness procedure

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Abstract: The present study examined whether pain catastrophizing and pain-related fear predict the experience of pain in body regions that are not targeted by an experimental muscle injury protocol. A delayed-onset muscle soreness (DOMS)-protocol was used to induce pain unilaterally in the pectoralis, serratus, trapezius, latisimus dorsi, and deltoid muscles. The day following the DOMS-protocol, participants were asked to rate their pain as they lifted weighted canisters with their targeted arm (i.e. injured) and their not-targeted arm. The lifting task is a non-noxious stimulus unless participants are already experiencing musculoskeletal pain. Therefore, reports of pain on the not-targeted arm were operationalized as pain in response to a non-noxious stimulus. Eighty-two (54 females, 28 males) healthy university students completed pain catastrophizing and fear of pain questionnaires and went through the DOMS-protocol. The analyses revealed that catastrophizing and pain-related fear prospectively predicted pain experience in response to a non-noxious stimulus. The possible mechanisms underlying this effect and clinical implications are discussed.

Perspective: Pain catastrophizing, and fear of pain prospectively predict the pain experience in response to a non-noxious stimulus. The pattern of findings is consistent with the predictions of current models of generalization of pain-related fear.

1. Introduction

Multisite pain (MSP) is more common than single-site pain [7, 26, 42], affecting 5-10% of the population [11]. Compared to single-site pain, MSP is associated with higher pain intensity, functional disability, and duration of pain complaints [9, 46]. The debilitating and treatment-resistant nature of MSP has led to increasing calls for the identification of risk factors [2, 25].

Numerous investigations suggest that pain catastrophizing [18, 22, 28] and pain-related fear [16, 38, 39] might be implicated in the development of MSP following musculoskeletal injury. Pain catastrophizing refers to a negative cognitive-affective response to actual or anticipated pain [12, 44, 50]. Fear of pain refers to a distressing emotional affective experience aroused by impending pain [63].

Bortsov and colleagues [3] reported that MSP following a motor vehicle accident was more strongly related to pain catastrophizing than to crash characteristics or associated injury. Similarly, Sullivan and colleagues [49] found correlations between pain-related fear and the number of pain-sites following rear-collision motor vehicle accidents. Although findings from these clinical studies suggest that pain-related psychological variables augment the risk of developing MSP, their correlational nature precludes strong statements regarding causality.

In a previous study, we examined the 'antecedent' status of pain catastrophizing and pain-related fear for the 'spreading' of pain following experimental muscle injury [41]. A delayed-onset muscle soreness (DOMS)-protocol was used to induce pain in the muscles of the upper arms and shoulders. We assessed pain catastrophizing and pain-related fear prior to the DOMS-induction, and pain distribution 24 hours later. The results showed that pain catastrophizing and pain-related fear independently predicted the number of pain sites reported following DOMS, including pain in regions distal from the muscles targeted by the DOMS-protocol.

Assuming that the prospective relations between pain catastrophizing, pain-related fear and MSP are replicable; questions arise concerning the pathways by which these psychological variables impact on the spreading of pain. There are at least two possibilities. Catastrophizing or fear might be associated with physical injury-characteristics, contributing to the spreading of pain [6, 20, 40]. Alternatively, generalization

of pain-related fear may increase pain in injury-free body sites, through activation of brain areas responsible for pain hyperalgesia [30, 31, 45].

Our first objective was to replicate previous findings [41] showing a prospective relationship between pain-related psychological variables and MSP. The second objective was to bring greater precision to the specification of processes underlying psychological influences on MSP. An important innovative design feature of the current study is increased anatomical precision of the DOMS-induction procedure. We used a DOMS-protocol that targeted muscles of the upper arm and shoulders unilaterally, allowing us to assess the pain experienced in anatomically distinct regions that remained injury-free following DOMS. The following day, participants were asked to lift a 3.6kg weight with their experimentally 'injured' arm, and their 'non-injured' arm. An important characteristic of the protocol is that, in the absence of muscle injury on the not-targeted arm, lifting a 3.6kg weight is not typically experienced as a noxious stimulus. Of interest was whether psychological variables would be associated with the experience of pain in muscle regions contralateral to the side of the experimentally 'injured' muscles. In the complete absence of tissue damage, there would be little basis to argue injury-related responses would be responsible for the experience of pain in muscle regions contralateral to those targeted by the DOMS-protocol. However, models of generalization of pain-related fear would predict that, through activation of brain networks associated with hyperalgesia, pain experience could spread from an injury site to an adjacent but injury-free area, even if the stimulus is not one that would be expected to generate a pain response [23, 24, 33].

2. Methods

Participants

We used a convenience sample of 82 (54 women, 28 men) healthy participants with a mean age of 23.2 years (*SD* = 5.15; range: 18 - 44 years). Participants were recruited through advertisements placed in the classifieds section of the McGill University website. A standardized telephone interview was used to screen participants for the exclusion criteria. Individuals were not considered for participation if they (1) had a medical condition that could be aggravated by participation in this study, (2) suffered from a

chronic pain condition, (3) were currently experiencing joint or muscle problems, (4) had engaged in resistance training of upper body or trunk muscles more than once per week in the 6 months prior to participation, or (5) had consumed pain relief medication in the five days prior to the testing session. The Physical Activity Readiness Questionnaire (PAR-Q) was used as a screening measure for potential contraindications to participation in the DOMS-induction procedure. The PAR-Q screens for the presence of factors that are linked to increased health risk when engaging in strenuous activity (e.g. shortness of breath, muscle or joint problems, fainting, circulatory problems). Participants endorsing any item on the PAR-Q were excluded from participation in the study [56].

Procedure

Ethical approval was obtained from the Institutional Review Board at McGill University. Participants were invited to the laboratory for two testing sessions scheduled 24 hours apart. Upon arrival to the laboratory, each participant provided informed consent. Participants were told that the study was aimed at investigating psychological and physical factors associated with pain after repeated physical activity. Anthropometric measures were obtained and participants were asked to complete the Pain Catastrophizing Scale (PCS) [52], and the Fear of Pain Questionnaire-III (FPQ) [37]. See Figure 1 for an overview of activities during sessions 1 and 2.

Standardized lifting task. For the lifting task participants stood in front of a stool to lift an unmarked 4-litre size paint canister partially filled with sand, weighing 3.6 kg. The height of the stool on which the canister was placed was adjusted such that the top of the canister was 5 cm below participants' standing wrist height. Participants were instructed to lift the canister three times per arm in a pre-determined sequence. Participants lifted the canister in a forward lateral movement until they reached an extension of 135 degrees of their arm and replaced the canister on the stool. Immediately after the lift, participants verbally rated how much pain they experienced during the lift on a numerical rating scale (NRS) from 0 to 10, with 0 'no pain' and 10 'excruciating pain'. For reference purposes the NRS was placed on the wall facing the participants. Whether participants began the lifting sequence with their dominant or non-dominant arm was randomized. Hand dominance was determined by verbal report. The

experimenter modeled the lift of the canister in order to minimize inter-individual variations in the approach to the lifting task. The experimenter modeled the canister lift without actually lifting the canister itself. A standardized power-point presentation guided participants through the procedure to ensure standardized intervals. Pauses between lifts were set at 8 seconds.

DOMS-protocol. The procedure used to induce DOMS consisted of four different strength exercises (i.e. chest fly, seated cable row, shoulder flexion, and shoulder abduction) involving repeated eccentric muscle actions. The DOMS-protocol was modeled after procedures described by Udermann and colleagues [60] and Sullivan and colleagues [48], and was adapted for execution with one arm. The exercise protocol was performed using the K1 Strength Training System (Body Craft, Sunbury, OH, USA). All exercises were performed in sets of five repetitions. To ensure appropriate resistance, participants completed each eccentric contraction in time to a countdown, set to 10 seconds. Consistent with Sullivan and colleagues [48], participants were asked to complete the first set of repetitions without any additional weight to become familiarized with the testing apparatus. Then, after the completion of each set, additional weight was added. The weight was increased in steps of ten pounds until participants reached the point of volitional fatigue or completed ten sets [61]. Volitional fatigue was defined as the point at which the participant could no longer control the descent of the weight [21]. For each participant the relative intensity of the final set of repetitions was 80% of the estimated repetition max, which is defined as the amount of weight a person could only lift one time [48].

Participants were asked to perform the eccentric contractions with maximal effort and were given verbal encouragement during the contraction (e.g. ‘Good job’ or ‘Keep going’). A one-minute recovery period was provided between each set. Breaks of two minutes between exercises were implemented to avoid muscle fatigue. To ensure performance of resisted eccentric contractions only, the experimenter moved the load for the participants on the return from full flexion. The emphasis on the eccentric portion of the strength exercise is known to induce DOMS [8]. During an eccentric contraction (lengthening contraction), the muscle elongates while under tension due to an opposing force, which causes

microtrauma to the muscle fibers. Peak exercise-induced DOMS has been noted to occur 24-48 hours after DOMS-induction [5].

To induce DOMS in the pectoralis major and serratus anterior muscles a chest fly was used. This exercise involves lying face-up on a horizontal bench, with buttocks on the bench, back flat on the bench, and feet flat on the ground. Participants grasped a cable attachment at shoulder width while keeping their elbow in a slight bend and lowered their arm out the side in a wide arc until their upper arm was parallel to the ground. The seated cable row works the middle trapezius and latisimus dorsi muscles. Participants sat facing the machine, gripping a pulley with their elbow at 90 degrees. While puffing out the chest participants released the pulley forward until their arms were fully extended. To target the anterior deltoid muscles participants performed a shoulder flexion. Participants stood with a straight back, legs slightly apart holding a cable attachment in their hand. Starting with the arm raised slightly above horizontal out to their side, participants lowered the cable attachment until it rested against their thighs. Lastly, to target the upper trapezius and middle deltoid muscles, participants performed a shoulder abduction. Participants were instructed to stand with their feet slightly apart, holding a cable attachment raised to eye level. The cable attachment was lowered until it rested against the front of participants' thighs. Mean number of performed sets for the chest fly was 5.90 (1.14), the seated cable row was 6.67 (1.3), the shoulder abduction was 4.05 (0.74), and the shoulder flexion was 3.8 (0.79). At the conclusion of the protocol, participants were asked to abstain from physical exercise and use of pain or anti-inflammatory medication prior to the next session, unless experiencing significant discomfort. None of the participants reported use of pain or anti-inflammatory medication.

Second testing session. The second testing session occurred 24 hours (±3 hours) after the first testing session, as done in previous studies [58]. During this session, the height of the stool was adjusted as in session 1, and participants were asked to repeat the lifting task. Finally, participants were debriefed.

Self-report measures. All questionnaires were completed at the end of the first testing session. The PCS was used to measure catastrophic pain-related cognitions. Participants indicated the frequency with which they experienced each of 13 different thoughts and feelings when in pain. Ratings were made

on a five-point scale with the endpoints '0' (not at all) and '4' (all the time). The PCS comprises three inter-related dimensions: magnification, rumination, and helplessness [4, 48, 50, 57]. Magnification refers to an exaggeration of the threat value of the pain stimulus (e.g. 'I become afraid that the pain will get worse'), rumination describes the inability to shift attention away from pain-related thoughts (e.g. 'I anxiously want the pain to go away'), and helplessness refers individuals' negative evaluation of their ability to cope effectively with painful stimuli (e.g. 'I feel I can't go on') [53]. Total scores range from 0 to 52, with higher scores indicating higher levels of pain catastrophizing. The total score reliably covers all facets of catastrophizing in the context of pain [53]. Research has supported the reliability and validity of the PCS [27, 52]. The Fear of Pain Questionnaire-III was used to assess pain-related fears. The FPQ is a 30-item self-report instrument describing different painful situations. Respondents are asked to rate how fearful they are of experiencing the pain associated with each situation described in the item content (e.g. 'Having one of your teeth drilled'). Fear ratings are made on a 5-point scale with the endpoints '1' (not at all) and '5' (extreme). Total scores (range 30–150) were calculated, whereby higher scores represent more fear. The FPQ comprises three subscales, minor pain (e.g. 'Getting a paper-cut on your finger'), severe pain (e.g. 'Breaking your leg'), and medical pain (e.g. 'Receiving an injection in your hip/buttocks'). Research has supported the reliability and validity of the FPQ [37].

Data analysis overview

Descriptive statistics were computed on sample characteristics and questionnaire scores. T-tests for independent samples were used to examine sex differences on demographic and dependent measures. We predicted that scores on the measures of pain catastrophizing and pain-related fear would prospectively predict the experience of pain on the not-targeted arm at session 2. Multilevel modeling was used to test whether there was a linear change in pain ratings on the not-targeted arm for each session, depending on individuals' levels of pain catastrophizing and pain-related fear, after controlling for pain on the targeted arm. To test these research questions, we defined two multilevel regression models. The first model tests the effects of pain catastrophizing, and the second model examines the influence of pain-related fear. A detailed description of both multilevel regression models can be found in the online

supplementary material. The effects included in each model were estimated simultaneously using the SAS procedure MIXED [62]. Explained variance was computed as the squared correlation between observed and predicted values for the dependent variable. Predicted values for the outcome measure are based on the estimated regression model and on the estimated values for the random effects. For the estimation of variance parameters we used the restricted maximum likelihood (REML) method of the SAS procedure MIXED [34]. Follow-up contrasts were calculated to test our a priori hypotheses.

3. Results

3.1 Sample characteristics. Table 1 presents the means and standard deviations for participants' demographics and pain-related psychosocial measures. There were no significant sex differences for age, (t (78) = -1.2, p=.23), and scores on measures of pain catastrophizing, (t (80) = 1.02, p=.31), while women reported significantly higher scores on indices of pain-related fear than men, (t (76) = 2.8, $p <$ .01). Furthermore, scores on an index of pain catastrophizing were significantly correlated with scores on pain-related fear. Scores on the PCS and the FPQ were comparable to those that have been reported in previous studies using pain-free non-clinical samples [37, 51, 54, 55]. Supplementary Table 1 presents an overview of the number of participants scoring within a certain range of pain catastrophizing and pain-related fear. It is apparent from this table that 4 participants scored more than 2 SD above the mean on the PCS, while 0 participants scored less than 2 SD below the mean. For the FPQ, 1 participant scored more than 2 SD above the mean and 4 participants scored less than 2 SD below the mean.

3.2. Manipulation check: DOMS-induction. Tests of simple effects revealed that while DOMS was effective in increasing mean reported pain on the targeted arm (pre: M = 2.25, SD = 2.13; post: M = 3.73, SD = 2.34, t(81) = -8.50, $p < .01$), the DOMS-induction did not influence mean reported pain for the not-targeted arm (pre: M = 2.44, SD = 2.19; post: M = 2.38, SD = 2.03, t(81) = 0.37, p = .72). The majority of participants would be considered to be experiencing mild to moderate pain at session 2 on their targeted arm. Participants' reported pain intensity ratings at session 2 were comparable to those that have been reported in previous research using DOMS protocols in non-clinical samples [14, 15, 41].

Furthermore, following the DOMS-induction participants reported, on average, more pain on their targeted arm than on their not-targeted arm (not-targeted: $M = 2.38$, $SD = 2.03$; targeted: $M = 3.73$, $SD = 2.34$, $t(81) = -9.73$, $p < .01$)

3.3.1 The role of pain catastrophizing in the prediction of pain on the not-targeted arm. A multilevel regression analysis was conducted to examine the contribution of pain catastrophizing to the prediction of reported pain on the not-targeted arm at session 1 and 2 (Model A). This model assumes that pain ratings for the not-targeted arm change linearly over subsequent lifts (1,2,3) within sessions 1 and 2 and that the linear change depends on the participant's pain catastrophizing level. Furthermore, pain reported on the targeted arm in the corresponding session was entered as a covariate to the model and made a significant contribution to the prediction of pain ratings on the not-targeted arm in both sessions. The estimated coefficient for the covariate indicated that participants who experienced higher levels of pain on the targeted arm also reported more intense pain on the not-targeted arm both in session 1 ($\beta_A^{(1)} = .79, p < .001$) and session 2 ($\beta_A^{(2)} = 0.99$, $p < .001$).

As shown in Table 2, there was no interaction between the linear trend of the change in pain ratings at session 1 over subsequent lifts and levels of pain catastrophizing. There was, however, a main effect of catastrophizing, which indicated that higher levels of pain catastrophizing predicted greater levels of pain on the first lift at session 1 ($\beta_{PCS}^{(1)} = 0.46$, $p < .01$) – when actually the lifting task was not expected to be painful. Given that pain was reported on a scale of 0 to 10, with a SD of 2.16, the results can be interpreted as follows: a change of 1 SD in PCS score was associated with an increase of 0.21 SD in reported pain on the first lift at session 1. Follow-up analyses revealed that high pain catastrophizers (i.e., 2 SD above average) reported greater pain than low pain catastrophizers (i.e., 2 SD below average) on the first lift ($M = 1.8$, $SD = 0.68$, $t(322) = 2.66$, $p < .01$), second lift ($M = 1.78$, $SD = 0.66$, $t(322) = 2.69$, $p < .01$) and third lift ($M = 1.75$, $SD = 0.68$, $t(322) = 2.57$, $p < .05$) of the first session.

At session 2, the linear change in reported pain intensity changed as a function of participants' pain catastrophizing scores (see Figure 2). Further analyses revealed that the slope of the linear trend of

the pain-ratings for the not-targeted arm at session 2 increased significantly for individuals with high levels of pain catastrophizing (mean PCS +2SD, $\beta_T + 2\beta_{TxPCS}$ = 0.53, p <.001; increase of 0.25 SD per trial), while for participants with relatively low levels of pain catastrophizing the reported pain on the not-targeted arm at session 2 did not significantly increase across trials (mean PCS - 2SD , $\beta_T - 2\beta_{TxPCS}$ = -0.17, p =.07; decrease of 0.08 SD per trial). Follow-up analyses revealed that there were no differences between high and low catastrophizers (i.e., 2 SD above average versus 2 SD below average) on the first (M= 0.31, SD = 0.61, t(322) = 0.51, p = .61) and second lift (M= 1.00, SD = 0.59, t(322) = 1.7, p = .09) at session 2, while high catastrophizers reported significantly greater pain during lift three at session 2 (M= 1.7, SD = 0.61, t(322) = 2.78, p < .01).

Comparison of the slopes for the linear change in reported pain intensity between session 1 and session 2 for the not-targeted arm revealed that high catastrophizers showed a significantly steeper slope at session 2, while low catastrophizers changed from a positive slope at session 1 to a zero slope at session 2. The findings imply that high pain catastrophizers' pain increased over repeated lifts with their not-targeted arm at session 2, while low catastrophizers reported similar levels of pain for all lifts.

3.4.2 The role of pain-related fear in the prediction of pain on the not-targeted arm. Model B followed the same assumptions as model A and examined the contribution of pain-related fear to the prediction of reported pain on the not-targeted arm at session 1 and 2. In Model B, pain reported on the targeted arm in the corresponding session was also entered as a covariate and made a significant contribution to the prediction of pain ratings on the not-targeted arm in both sessions. The estimated coefficient of the covariate in session 1 ($\beta_A^{(1)} = .77, p < .001$) and session 2 ($\beta_A^{(2)} = .98, p < .001$) indicated that participants who experienced higher levels of pain on the targeted arm also tended to report more intense pain on the not-targeted arm.

As shown in Table 3, there was no interaction between the linear trend of the change in pain ratings at session 1 over subsequent lifts and levels of pain-related fear. In other words, the slopes of the linear trends for varying levels of pain-related fear were parallel. There was, however, a main effect of

pain-related fear, which indicated that higher levels of pain-related fear predicted greater levels of pain on the first lift at session 1 ($\beta_{FOP}^{(1)}$ = 0.74, p < .0001; a change of 1 SD in pain-related fear score was associated with an increase of 0.34 SD in reported pain on the first lift at session 1). Follow-up analyses revealed that individuals with high pain-related fear (i.e., 2 SD above average) reported greater pain on the first lift (*M*= 2.96, *SD* = 0.69, *t*(306) = 4.3, p < .0001), second lift (*M*= 2.82, *SD* = 0.68, *t*(306) = 4.17, p < .0001), and third lift (*M*= 2.68, *SD* = 0.7, *t*(306) = 3.81, p < .0005) than individuals with low pain-related fear (i.e., 2 SD below average).

For session 2, the multilevel regression analysis revealed a significant interaction effect between the linear trend of pain ratings during the lifting task and fear of pain scores (see Figure 3). Similar to the findings of Model A, the interaction effect indicated that the slope of the linear trend for the pain ratings on the not-targeted arm at session 2 varied as a function of levels of pain-related fear. Further analyses revealed that the slope of the linear trend of pain ratings for the not-targeted arm at session 2 increased significantly for individuals with high levels of pain-related fear (mean pain-related fear +2 SD, β_T + $2\beta_{TxFPQ}$ = 0.47, p < .001; increase of 0.22 SD per trial), while the reported pain on the not-targeted arm at session 2 did not change significantly across trials for participants with relatively low levels of pain-related fear (mean pain-related fear -2 SD, β_T - $2\beta_{TxFPQ}$ = -0.06, p = .48; decrease of 0.03 SD per trial). Follow-up analyses revealed that there was no difference between subjects with high and low pain-related fear on the first lift at session 2 (*M*= 1.01, *SD* = 0.66, *t*(306) = 1.55, p = .12), while subjects with high pain-related fear reported significantly greater pain during lifts two (*M*= 1.55, *SD* = 0.64, *t*(306) = 2.41, p < .05) and three (*M*= 2.08, *SD* = 0.67, *t*(306) = 3.12, p < .01) at session 2 than subjects with low pain-related fear.

Comparison of the slopes for the linear change in reported pain intensity between session 1 and session 2 revealed that subject with high pain-related fear showed a significantly steeper slope at session 2, while subjects with low pain-related fear change from a positive slope at session 1 to a zero slope at session 2.

Note that both model A and B performed rather well in predicting participants' pain ratings for the not-targeted arm after DOMS induction, as they explained respectively 96.4% and 96.3% of the variance in this variable. Furthermore, including random intercepts in the model to account for different average pain ratings across subjects for the not-targeted arm at the first trials of sessions 1 and 2 was clearly important, given that for each model, a considerable part of the variability on this variable was due to differences between subjects. Indeed, for model A, 89% and 87% of the variability in the pain ratings at the first trial of session 1 and session 2 respectively, were due to differences between subjects. Likewise, 88% and 86% of the variability in the pain ratings at the first trial of session 1 and session 2 respectively, were due to individual differences for model B.

4. Discussion

The aim of the current study was to elucidate whether pain catastrophizing and pain-related fear predict the verbal report of pain in body parts contralateral to those targeted by the DOMS-protocol. The findings of the present study join a growing body of literature supporting the view that pain catastrophizing and pain-related fear increase the risk of experiencing adverse pain outcomes. To date, experimental research has focused on bringing greater precision to the specification of processes underlying psychological influences on the experience of pain within the experimentally injured body parts [41, 48, 59]. The results of the present study extend previous findings in showing that pain catastrophizing and pain-related fear, measured in a pain-free state, also augment the experience of pain in response to non-noxious stimuli, as the canister lifting task is not painful unless the individual is already experiencing musculoskeletal pain.

As expected, the DOMS-protocol caused an increase in pain on the targeted arm. The muscles on the not-targeted arm engaged during the canister lifting were unaffected by the DOMS-protocol and the strain of the lifting task at session 2 was identical to the previous session. Despite this, reported pain in response to the canister lift with the not-targeted arm in session 2 increased across lifts, at a significantly greater rate than session 1. Due to the within subject nature of the experiment, there is little basis for suggesting that processes other than the pain increase on the targeted arm were responsible for the

increasing pain reports during the lifting task on the not-targeted arm at session 2. Furthermore, the extent to which pain on the not-targeted arm changed over time was influenced by pain catastrophizing and pain-related fear. These interactions were present only at session 2, whereby high levels of pain catastrophizing and pain-related fear predicted increasing pain over successive lifts, and low levels predicted flat or decreasing trends. Interestingly, high and low fear and pain catastrophizing individuals reported similar pain intensities during the first lift on their not-targeted arm at session 2; however, while pain dissipated over time among low fear and low pain catastrophizers, leaving them with pain only in targeted body sites, those scoring high continued to report increasing mild to moderate levels of pain in not-targeted, as well as targeted areas.

Recently, researchers have speculated about the peripheral and central mechanisms that could lead to the experience of pain in the absence of noxious stimulation. Recent research has suggested the 'generalization' of pain-related fear as a mechanism by which fear might contribute to the experience of pain in body parts distal to the site of injury [16, 38, 39, 41]. Generalization of pain-related fear occurs when the expectation of a painful sensation and pain-related fear is associated with a stimulus that resembles (lifts on not-targeted arm), but is not identical to, the original pain-provoking stimulus (lifts on targeted arm) [16]. Research has shown that the fear-induced expectation of a painful sensation contributes to an increased sensitivity to pain [10], through the activation of brain areas responsible for pain hyperalgesia [30, 31, 45]. Through generalization of pain-related fear, the expectation of pain may have generalized to lifts with the not-targeted arm, activated corresponding brain areas, and thereby led to reports of increasing pain. Lastly, highly fearful individuals generally have more negative expectations towards pain, such as predicting higher levels of pain [13, 36, 59], suggesting greater activation of brain areas associated with hyperalgesia.

Two issues deserve further inquiry. First, the assessment of pain-related fear generalization, which is not measured in the current study. To prove the involvement of the generalization of pain-related fear in the experience of increasing pain in not-targeted body sites, changes in pain on the not-targeted arm need to be mediated by pain-related fear. The second issue that deserves further inquiry is the

possible effect of pain expectancy. It is possible that high catastrophizers and high pain-related fear individuals did not correct their pain expectancies based on their preceding pain experiences, leading to increasing pain over the course of the lifts. Future studies should include measures of pain expectancy to further explore this issue.

Previous studies have suggested that pain-related fear might lead to muscle activation alterations aimed at protecting injured muscle tissue, which in turn lead to increased pain in surrounding muscle tissue [20, 35, 40]. In the absence of injury, there is little basis to suggest the presence of muscle activation alterations, which can therefore be ruled out as a mechanism by which pain may increase in not-targeted body parts.

The results of the current study suggest that pain catastrophizing predicts the experience of pain in response to a non-noxious stimulus in body sites not-targeted by experimentally induced injury. Pain catastrophizing has been hypothesized to affect the experience of pain in injury-free sites through its relationship with altered endogenous modulation of pain [18, 22, 28]. Pain catastrophizing has also been associated with indices of central sensitization [18, 43], whereby neuroplastic changes in the dorsal horn, enacted by repeated nociceptive stimulation, lead to an expansion of the receptive fields of nociceptors [32]. Expanded receptor fields may lead to the spreading of secondary hyperalgesia beyond the site of injury, thereby spreading nociceptive input into injury-free body parts [47]. Furthermore, high levels of pain catastrophizing are potentially associated with lower values on an index of descending inhibition [22]. Normally, in the presence of ongoing noxious stimulation, spinal cord responses to additional noxious stimuli are down-regulated in the brain, a modulatory response termed conditioned pain modulation [1, 65]. It should therefore have been expected that, with pain in one arm, stimulation of the canister lift on the not-targeted arm would be inhibited; however, due to potentially lower values on an index of descending inhibition, high catastrophizers reported increasing pain intensities over the canister lifts with their not-targeted arm.

Recent studies have suggested that the association between pain catastrophizing and an increased release of pro-inflammatory cytokines [17] might contribute to the spreading of pain beyond the site of

injury [6, 17]. While DOMS is a valid model for musculoskeletal injury, there have been reports suggesting that pro-inflammatory cytokines are not elevated following DOMS [29]. The absence of an increased release of pro-inflammatory cytokines following DOMS-induction therefore precludes effects of pain-catastrophizing through inflammatory mediators.

Caution must be used when interpreting the study findings. To maximize homogeneity of the study sample, several exclusion criteria were used, limiting its generalizability. Furthermore, while exercise-induced DOMS is a useful technique to mimic musculoskeletal pain conditions, it lacks the affective and traumatic components of musculoskeletal injuries. In addition, healthy undergraduates differ from individuals suffering from chronic pain on a number of demographic and health status variables. As such, the current sample includes few participants whose questionnaire scores divert more than 2 SD from the mean. Nevertheless, the fact that in very few participants robust and significant effects are found, can also be seen as a strength. It is reasonable to assume that these effects would only be stronger when individuals with more extreme questionnaire scores would have been included. Future research should focus on systematically selecting 'extreme' samples.

Lastly, the results of the current study might not be generalizable to MSP conditions that arise in the absence of injury such as arthritis or chronic widespread pain. Alongside the presence of pain in multiple sites, these conditions are also associated with developmental processes onset conditions, symptom profiles, and pathophysiology different from those produced by DOMS-protocols [19, 64].

The emerging body of findings raises the possibility that pain catastrophizing and pain-related fear might be risk factors for the experience of pain in response to non-noxious stimuli. These findings call for the inclusion of measures of pain catastrophizing and pain-related fear as screening measures for identifying individuals at risk for problematic outcomes following musculoskeletal injury. Currently, psychological interventions for individuals with MSP are typically offered only once the condition has become chronic. Targeting these variables in the early stages of treatment might decrease the probability of transitioning from acute pain to more serious chronic pain syndromes.

5. Conflict of interest statement

The authors report no conflict of interest.

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Figure 1

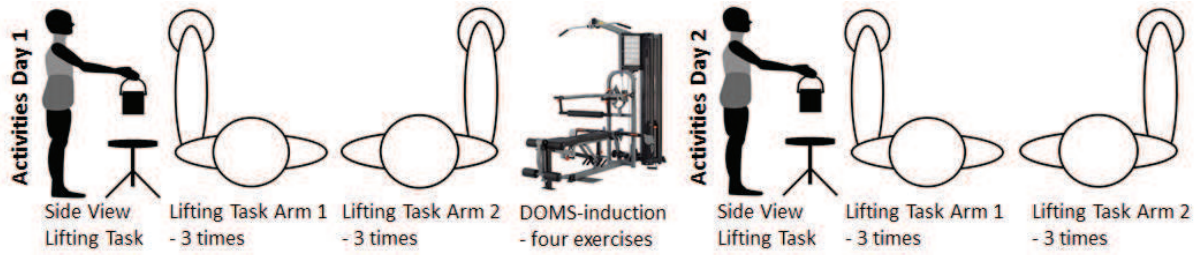

Figure 1. *Overview of activities throughout sessions 1 and 2.*

Note: This figure depicts the activities performed by participants at sessions 1 and 2. Please note that whether participants began the lifting sequence with their dominant or non-dominant arm was randomized.

Figure 2

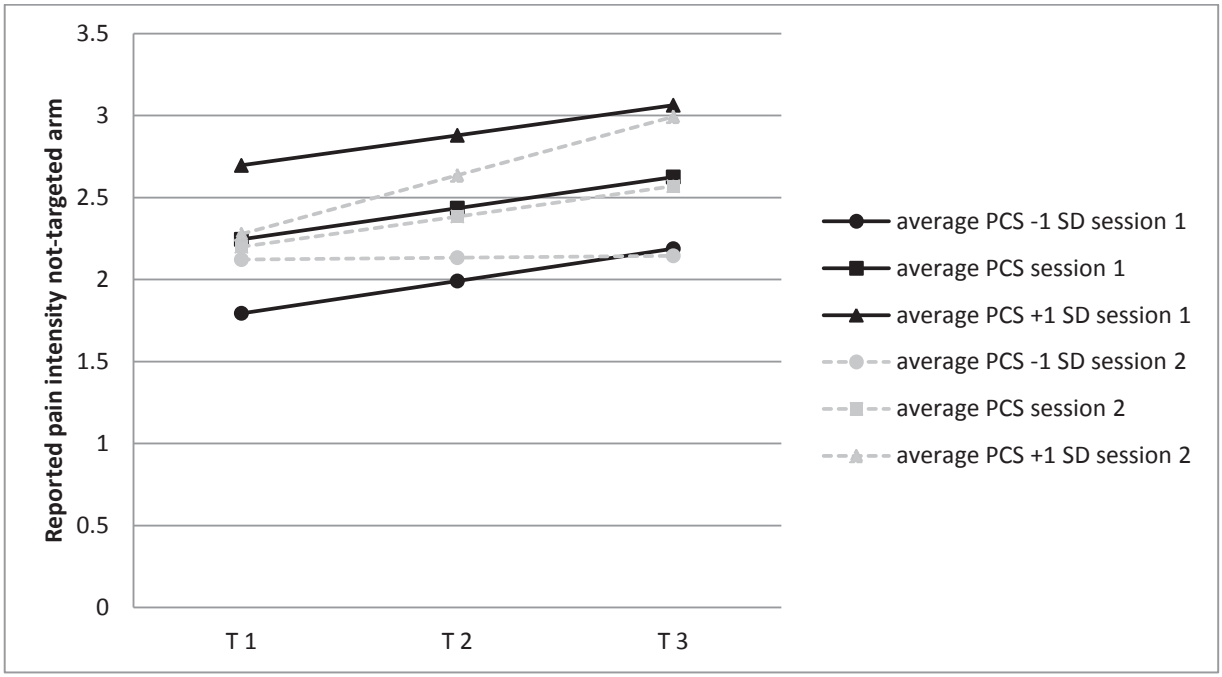

Figure 2. *Reported pain ratings for the not-targeted arm at session 1 and session 2, split up for high and low catastrophizers.*

Note: T1 = Trial 1; T2 = Trial 2; T3 = Trial 3;

Figure 3

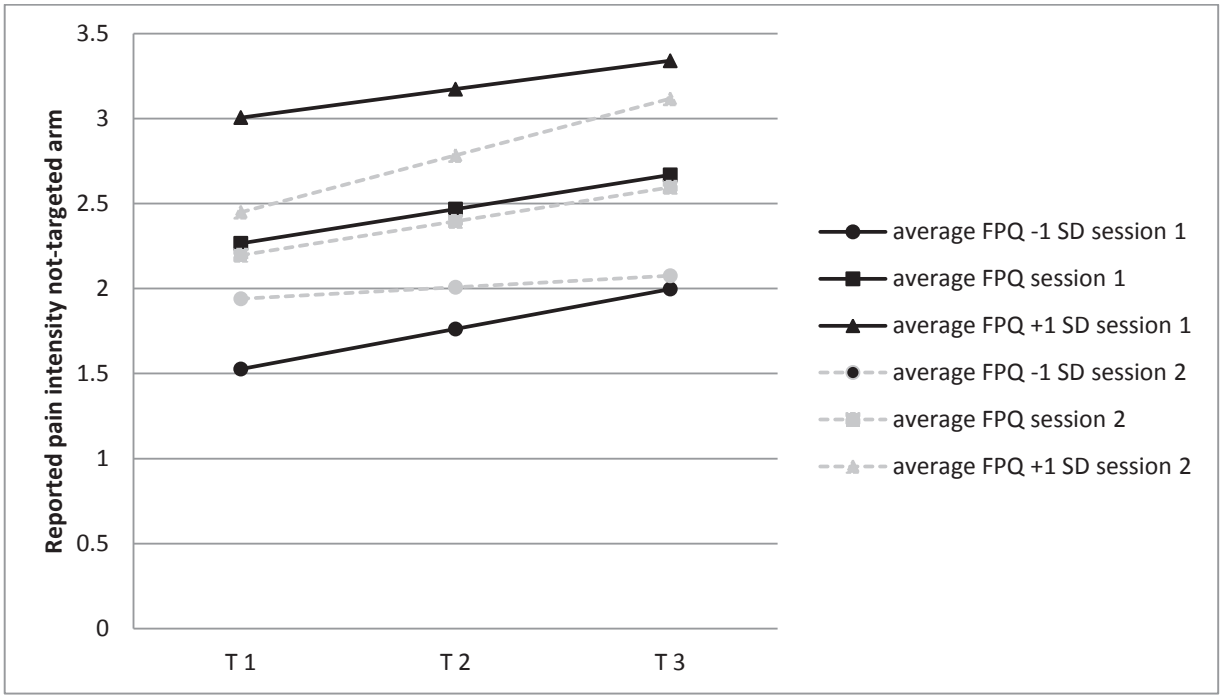

Figure 3. *Reported pain ratings for the not-targeted arm at session 1 and session 2, split up for high and low fear of pain.*

Note: T1 = Trial 1; T2 = Trial 2; T3 = Trial 3;

Table 1

Table 1. *Sample Characteristics*

Variables	Women (n = 54)	Men (n = 28)	*P* value
Age	22.7 (4.5)	24.2 (6.2)	$p = .23$
PCS	18.8 (10.2)	16.6 (7.4)	$p = .31$
FPQ	87.8 (18.3)	76.4 (14.2)	$p < .01$

Note: PCS: Pain Catastrophizing Scale; FPQ: Fear of Pain Questionnaire III;

Table 2. *Multilevel regression predicting pain ratings on the not-targeted arm at subsequent trials of at session 1 and 2 for varying levels of Pain Catastrophizing (PCS)*

Coef	Description effect	estimate	Standard error	p-value
$\mu^{(1)}$	Average pain rating at trial 1 of session 1 for average PCS and $Z_{ij1}^{A} = 0$	2.245	0.168	<.001
$\beta_{T}^{(1)}$	Average change in pain per trial of session 1 for participants with average PCS	0.19	0.042	<.001
$\beta_{PCS}^{(1)}$	Average change in pain rating at trial 1 of session 1 if PCS level increases by 1 SD	0.451	0.169	<.01
$\beta_{TxPCS}^{(1)}$	Change in slope of linear trend for pain ratings over trials of session 1 if PCS increases by 1 SD	-0.007	0.04	0.865
$\beta_{A}^{(1)}$	Average increase in pain rating at session 1 if Z_{ij1}^{A} increases one SD	0.794	0.097	<.001
$\mu^{(2)}$	Average pain rating at trial 1 of session 2 for average PCS	2.2	0.151	<.001
$\beta_{T}^{(2)}$	Average change in pain rating per trial of session 2 for participants with average PCS	0.185	0.041	<.001
$\beta_{PCS}^{(2)}$	Average change in pain rating at trial 1 of session 2 if PCS level increases by 1 SD	0.078	0.152	0.609
$\beta_{TxPCS}^{(2)}$	Change in slope of linear trend for pain ratings over trials of session 2 if PCS increases by 1 SD	0.173	0.039	<.001
$\beta_{A}^{(2)}$	Average increase in pain rating in session 2 if Z_{ij2}^{A} increases one SD	0.985	0.097	<.001
$\sigma_{(1)}^{2}$	Between subject variability in pain ratings at trial 1 of session 1	2.010	.464	<.001
$\sigma_{(2)}^{2}$	Between subject variability in pain ratings at trial 1 of session 2	1.637	.317	<.001
σ_{12}	Covariance of random intercepts of session 1 and 2	1.320	.316	<.001
σ_{ε}^{2}	Within subject variability in pain ratings	.249	.021	<.001
R^{2}	Explained proportion of variance in pain ratings	96.4%		

Coefficient	Description Effect	estimate	Standard error	p-value
$\mu^{(2)} - \mu^{(1)}$	Difference between average pain ratings at trial 1 of session 1 and session 2 at average PCS	-0.045	0.137	0.741
$\beta_T^{(2)} - \beta_T^{(1)}$	Difference in slope of linear trend for successive pain ratings at average PCS between session 2 and session 1	-0.006	0.057	0.923
$\mu^{(1)} - \beta_{PCS}^{(1)}$	Average pain rating at session 1 trial 1 for participants with PCS -1SD and $Z_{ij1}^{A} = 0$	1.794	0.24	<.001
$\mu^{(1)} - 2\beta_{PCS}^{(1)}$	Average pain rating at trial 1 for participants with PCS -2SD at session 1	1.343	0.379	<.001
$\mu^{(1)} + \beta_{PCS}^{(1)}$	Average pain rating at trial 1 for participants with PCS +1SD at session 1	2.696	0.238	<.001
$\mu^{(1)} + 2\beta_{PCS}^{(1)}$	Average pain rating at trial 1 for participants with PCS +2SD at session 1	3.147	0.377	<.001
$\beta_T^{(1)} - \beta_{TxPCS}^{(1)}$	Slope of linear trend of average pain rating for participants with PCS -1SD at session 1	0.197	0.056	<.001
$\beta_T^{(1)} - 2\beta_{TxPCS}^{(1)}$	Slope of linear trend of average pain rating for participants with PCS -2SD at session 1	0.204	0.088	0.021
$\beta_T^{(1)} + \beta_{TxPCS}^{(1)}$	Slope of linear trend of average pain rating for participants with PCS +1SD at session 1	0.183	0.0579	.002
$\beta_T^{(1)} + 2\beta_{TxPCS}^{(1)}$	Slope of linear trend of average pain rating for participants with PCS +2SD at session 1	0.177	0.091	.053
$\mu^{(1)} + 2\beta_T^{(1)} - \beta_{PCS}^{(1)} - 2\beta_{TxPCS}^{(1)}$	Average pain rating at trial 3 for participants with PCS -1SD at	2.188	0.238	<.001

	session 1			
$\mu^{(1)} + 2\beta_T^{(1)} - 2\beta_{PCS}^{(1)} - 4\beta_{TxPCS}^{(1)}$	Average pain rating at trial 3 for participants with PCS -2SD at session 1	1.75	0.378	<.001
$\mu^{(1)} + 2\beta_T^{(1)} + \beta_{PCS}^{(1)} + 2\beta_{TxPCS}^{(1)}$	Average pain rating at trial 3 for participants with PCS +1SD at session 1	3.063	0.241	<.001
$\mu^{(1)} + 2\beta_T^{(1)} + 2\beta_{PCS}^{(1)} + 4\beta_{TxPCS}^{(1)}$	Average pain rating at trial 3 for participants with PCS +2SD at session 1	3.5000	0.382	<.001
$\mu^{(2)} - \beta_{PCS}^{(2)}$	Average pain rating at trial 1 for participants with PCS -1SD at session 2	2.122	0.215	<.001
$\mu^{(2)} - 2\beta_{PCS}^{(2)}$	Average pain rating at trial 1 for participants with PCS -2SD at session 2	2.044	0.342	<.001
$\mu^{(2)} + \beta_{PCS}^{(2)}$	Average pain rating at trial 1 for participants with PCS +1SD at session 2	2.278	0.213	<.001
$\mu^{(2)} + 2\beta_{PCS}^{(2)}$	Average pain rating at trial 1 for participants with PCS +2SD at session 2	2.356	0.338	<.001
$\beta_T^{(2)} - \beta_{TxPCS}^{(2)}$	Slope of linear trend of average pain rating for participants with PCS -1SD at session 2	0.011	0.056	0.839
$\beta_T^{(2)} - 2\beta_{TxPCS}^{(2)}$	Slope of linear trend of average pain rating for participants with PCS -2SD at session 2	-0.162	-0.088	0.067
$\beta_T^{(2)} + \beta_{TxPCS}^{(2)}$	Slope of linear trend of average pain rating for participants with PCS +1SD at session 2	0.358	0.057	<.001
$\beta_T^{(2)} + 2\beta_{TxPCS}^{(2)}$	Slope of linear trend of average pain rating for participants with PCS +2SD at session 2	0.530	0.089	<.001
$\mu^{(2)} + 2\beta_T^{(2)} - \beta_{PCS}^{(2)} - 2\beta_{TxPCS}^{(2)}$	Average pain rating at trial 3 for participants with PCS -1SD at	2.144	0.213	<.001

	session 2			
$\mu^{(2)} + 2\beta_T^{(2)} - 2\beta_{PCS}^{(2)} - 4\beta_{TxPCS}^{(2)}$	Average pain rating at trial 3 for participants with PCS -2SD at session 2	1.72	0.339	<.001
$\mu^{(2)} + 2\beta_T^{(2)} + \beta_{PCS}^{(2)} + 2\beta_{TxPCS}^{(2)}$	Average pain rating at trial 3 for participants with PCS +1SD at session 2	2.993	0.216	<.001
$\mu^{(2)} + 2\beta_T^{(2)} + 2\beta_{PCS}^{(2)} + 4\beta_{TxPCS}^{(2)}$	Average pain rating at trial 3 for participants with PCS +2SD at session 2	3.418	0.343	<.001

Table 3. *Multilevel regression predicting pain ratings on the not-targeted arm at subsequent trials of session 1 and 2 for varying levels of Fear of Pain (FPQ)*

Coef	Description Effect	estimate	Standard error	p-value
$\mu^{(1)}$	Average pain rating at trial 1 of session 1 for average FPQ and $Z_{ij1}^{A} = 0$	2.266	0.166	<.001
$\beta_{T}^{(1)}$	Average change in pain per trial of session 1 for participants with average FPQ	0.201	0.044	<.001
$\beta_{FPQ}^{(1)}$	Average change in pain rating at trial 1 of session 1 if FPQ level increases by 1 SD	0.74	0.172	<.001
$\beta_{TxFPQ}^{(1)}$	Change in slope of linear trend for pain ratings over trials of session 1 if FPQ increases by 1 SD	-0.034	0.041	0.41
$\beta_{A}^{(1)}$	Average increase in pain rating at session 1 if Z_{ij1}^{A} increases one SD	0.772	0.103	<.001
$\mu^{(2)}$	Average pain rating at trial 1 of session 2 for average FPQ	2.196	0.153	<.001
$\beta_{T}^{(2)}$	Average change in pain rating per trial of session 2 for participants with average FPQ	0.201	0.043	<.001
$\beta_{FPQ}^{(2)}$	Average change in pain rating at trial 1 of session 2 if FPQ level increases by 1 SD	0.255	0.165	0.123
$\beta_{TxFPQ}^{(2)}$	Change in slope of linear trend for pain ratings over trials of session 2 if FPQ increases by 1 SD	0.133	0.041	<.01
$\beta_{A}^{(2)}$	Average increase in pain rating in session 2 if Z_{ij2}^{A} increases one SD	0.976	0.109	<.001
$\sigma_{(1)}^{2}$	Between subject variability in pain ratings at trial 1 of session 1	1.238	0.291	<.001
$\sigma_{(2)}^{2}$	Between subject variability in pain ratings at trial 1 on session 2	1.591	0.3	<.001
σ_{12}	Covariance of random intercepts of session 1 and 2	1.59	0.305	<.001
σ_{ε}^{2}	Within subject variability in pain ratings	0.261	0.022	<.001
R^{2}	Explained proportion of variance in pain ratings	96.3%		

Coefficient	Description Effect	estimate	Standard error	p-value
$\mu^{(2)} - \mu^{(1)}$	Difference between average pain ratings at trial 1 on session 1 and session 2 at average FPQ	-0.072	0.139	0.606
$\beta_T^{(2)} - \beta_T^{(1)}$	Difference in slope of linear trend for successive pain ratings at average FPQ between session 2 and session 1	-0.001	0.061	0.061
$\mu^{(1)} - \beta_{FPQ}^{(1)}$	Average pain rating on session 1 trial 1 for participants with FPQ -1SD and $Z_{ij1}^{A} = 0$	1.527	0.242	<.001
$\mu^{(1)} - 2\beta_{FPQ}^{(1)}$	Average pain rating at trial 1 for participants with FPQ -2SD on session 1	0.787	0.385	0.042
$\mu^{(1)} + \beta_{FPQ}^{(1)}$	Average pain rating at trial 1 for participants with FPQ +1SD on session 1	3.006	0.236	<.001
$\mu^{(1)} + 2\beta_{FPQ}^{(1)}$	Average pain rating at trial 1 for participants with FPQ +2SD on session 1	3.745	0.378	<.001
$\beta_T^{(1)} - \beta_{TxFPQ}^{(1)}$	Slope of linear trend of average pain rating for participants with FPQ -1SD on session 1	0.235	0.058	<.001
$\beta_T^{(1)} - 2\beta_{TxFPQ}^{(1)}$	Slope of linear trend of average pain rating for participants with FPQ -2SD on session 1	0.27	0.092	0.004
$\beta_T^{(1)} + \beta_{TxFPQ}^{(1)}$	Slope of linear trend of average pain rating for participants with FPQ +1SD on session 1	0.167	0.062	0.008
$\beta_T^{(1)} + 2\beta_{TxFPQ}^{(1)}$	Slope of linear trend of average pain rating for participants with FPQ +2SD on session 1	0.133	0.096	0.169
$\mu^{(1)} + 2\beta_T^{(1)} - \beta_{FPQ}^{(1)} - 2\beta_{TxFPQ}^{(1)}$	Average pain rating at trial 3 for participants with FPQ -1SD on session 1	1.998	0.239	<.001
$\mu^{(1)} + 2\beta_T^{(1)} - 2\beta_{FPQ}^{(1)} - 4\beta_{TxFPQ}^{(1)}$	Average pain rating at trial 3 for participants with FPQ -	1.327	0.385	<.001

	2SD on session 1			
$\mu^{(1)} + 2\beta_T^{(1)} + \beta_{FPQ}^{(1)} + 2\beta_{TxFPQ}^{(1)}$	Average pain rating at trial 3 for participants with FPQ +1SD on session 1	3.339	0.246	<.001
$\mu^{(1)} + 2\beta_T^{(1)} + 2\beta_{FPQ}^{(1)} + 4\beta_{TxFPQ}^{(1)}$	Average pain rating at trial 3 for participants with FPQ +2SD on session 1	4.010	0.394	<.001
$\mu^{(2)} - \beta_{FPQ}^{(2)}$	Average pain rating at trial 1 for participants with FPQ -1SD on session 2	1.94	0.229	<.001
$\mu^{(2)} - 2\beta_{FPQ}^{(2)}$	Average pain rating at trial 1 for participants with FPQ -2SD on session 2	1.685	0.368	<.001
$\mu^{(2)} + \beta_{FPQ}^{(2)}$	Average pain rating at trial 1 for participants with FPQ +1SD on session 2	2.449	0.221	<.001
$\mu^{(2)} + 2\beta_{FPQ}^{(2)}$	Average pain rating at trial 1 for participants with FPQ +2SD on session 2	2.704	0.359	<.001
$\beta_T^{(2)} - \beta_{TxFPQ}^{(2)}$	Slope of linear trend of average pain rating for participants with FPQ -1SD on session 2	0.068	0.059	0.252
$\beta_T^{(2)} - 2\beta_{TxFPQ}^{(2)}$	Slope of linear trend of average pain rating for participants with FPQ -2SD on session 2	-0.065	0.092	0.481
$\beta_T^{(2)} + \beta_{TxFPQ}^{(2)}$	Slope of linear trend of average pain rating for participants with FPQ +1SD on session 2	0.333	0.06	<.001
$\beta_T^{(2)} + 2\beta_{TxFPQ}^{(2)}$	Slope of linear trend of average pain rating for participants with FPQ +2SD on session 2	0.466	0.093	<.001
$\mu^{(2)} + 2\beta_T^{(2)} - \beta_{FPQ}^{(2)} - 2\beta_{TxFPQ}^{(2)}$	Average pain rating at trial 3 for participants with FPQ -1SD on session 2	2.075	0.222	<.001
$\mu^{(2)} + 2\beta_T^{(2)} - 2\beta_{FPQ}^{(2)} - 4\beta_{TxFPQ}^{(2)}$	Average pain rating at trial 3 for participants with FPQ -	1.555	0.362	<.001

	2SD on session 2			
$\mu^{(2)} + 2\beta_T^{(2)} + \beta_{FPQ}^{(2)} + 2\beta_{TxFPQ}^{(2)}$	Average pain rating at trial 3 for participants with FPQ +1SD on session 2	3.116	0.23	<.001
$\mu^{(2)} + 2\beta_T^{(2)} + 2\beta_{FPQ}^{(2)} + 4\beta_{TxFPQ}^{(2)}$	Average pain rating at trial 3 for participants with FPQ +2SD on session 2	3.636	0.372	<.001

Tables Online supplementary material

Online supplementary material

To describe the model we assume that Y_{ijk}^{NA} represents the reported pain rating of subject *i (i=1,..,82)* on trial *j (j=1,2,3)* at session *k (k=1,2) for the not-targeted arm*. To study to what extent pain generalization from the targeted arm to the not-targeted arm depends on the PCS score of the subject and on the pain rating reported for the targeted arm, we use the following multilevel model:

$$Y_{ijk}^{NA} = \mu^{(k)} + \theta_i^{(k)} + \beta_T^{(k)} T_j + \beta_{PCS}^{(k)} PCS_i + \beta_{TxPCS}^{(k)} T_j PCS_i + \beta_A^{(k)} Z_{ijk}^A + \varepsilon_{ijk}$$

The model assumes that pain ratings for the not-targeted arm change linearly in subsequent trials. The linear trend variable T_j (which equals 0,1,2 at trials 1,2,3) is used to model a linear trend for the reported pain ratings on the not-targeted arm at session *k*. Furthermore, the variable $\beta_{PCS}^{(k)}$ denotes the standardized PCS score of subject *i* and the variable Z_{ijk}^A represents the standardized value of pain ratings on the targeted arm at session *k*. The parameter $\mu^{(k)}$ represents the average value of the dependent variable at trial 1 at session *k* for subjects with an average PCS score (i.e. PCS=0) and average Z_{ijk}^A $(i.e. Z_{ijk}^A = 0)$. Finally, random intercepts $\theta_i^{(1)}$ and $\theta_i^{(2)}$ are included to model subject differences in the reported pain ratings for the not-targeted arm at trial 1 at sessions 1 and 2, respectively. The vector of random intercepts $(\theta_i^{(1)}, \theta_i^{(2)})$ is assumed to have a bivariate normal distribution with mean (0,0), variance $(\sigma_{(1)}^2, \sigma_{(2)}^2)$ and covariance σ_{12}. The error term $\varepsilon_{ijk} \sim N(0, \sigma_\varepsilon^2)$ captures the effect of other variables that may affect the dependent variable but which are not included in the model.

The model coefficients should be interpreted as follows:

$\mu^{(k)}$= Average baseline corrected pain rating at trial 1 at session *k* on the not-targeted arm for subjects with an average PCS score (i.e. $\beta_{PCS}^{(k)} = 0$), with an average pain rating on the targeted arm at session $(i.e. Z_{ijk}^A = 0)$, and with an average random intercept value for session k (i.e. $\theta_i^{(k)} = 0$).

$\beta_T^{(k)}$= Average change in pain rating for the not-targeted arm at subsequent trials at session k for subjects with an average PCS score (i.e. PCS=0).

$\beta_{PCS}^{(k)}$= Average change in pain ratings for the not-targeted arm at trial 1 at session k due to an increase of one SD for the PCS score.

$\beta_{TxPCS}^{(k)}$= Interaction effect between the linear trend and the standardized PCS score. This effect represents the change in the slope of the linear trend if the PCS score increases one standard deviation at session k.

$\beta_{A}^{(k)}$= Average increase in the pain rating at session k if the pain rating on the targeted arm at session k increases one SD.

$\sigma_{(k)}^{2}$=variance of the subject-specific predicted pain ratings on the not-targeted arm at trial 1 for session k.

σ_{ε}^{2}=variance of the error term

Note: This model is described in exemplifying detail, while the models testing the effects of pain-related fear follow the same layout.

Supplementary Table 1

Supplementary Table 1. *Overview of number of participants scoring within a certain range of standardized predictor variables.*

	PCS	FPQ
Higher than+2 SD	4	1
between +1SD and +2 SD	6	13
between 0SD and +1SD	28	26
between -1SD and 0SD	31	24
between -2SD and -1SD	13	14
Lower than -2 SD	0	4